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<p>(21) International Application Number: PCT/HU94/00012</p> <p>(22) International Filing Date: 9 May 1994 (09.05.94)</p> <p>(30) Priority Data: P 93 01373 12 May 1993 (12.05.93) HU</p> <p>(71) Applicant (for all designated States except US): CHINOIN LTD. [HU/HU]; Tó u. 1-5, H-1045 Budapest (HU).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): SZENTE, Lajos [HU/HU]; Gombocz Z. u. 17, H-1118 Budapest (HU). SZEJILI, József [HU/HU]; Rákos u. 8, H-1028 Budapest (HU). VIKMON, Andrásné [HU/HU]; Endrőri S. u. 24, H-1026 Budapest (HU).</p> <p>(74) Common Representative: CHINOIN LTD.; Dept. for Industrial Property Rights, Tó u. 1-5, H-1045 Budapest (HU).</p>	<p>(81) Designated States: AT, AU, BE, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
(54) Title: INCLUSION COMPLEXES OF TAXOL OR TAXOTERE OR TAXUS EXTRACT FORMED WITH CYCLODEXTRINS, ITS PREPARATION AND USE		
<p>(57) Abstract</p> <p>The invention relates to the inclusion complexes of Taxol or Taxotere and Taxus extracts (comprising besides taxol other diterpene taxan-derivatives) formed with a cyclodextrin derivative or cyclodextrin-derivative-mixture. According to the invention, improved aqueous solubility of Taxol and Taxan-derivatives can be reached by using suitable cyclodextrins and/or cyclodextrin derivatives and/or mixtures thereof. The inclusion complexes can be prepared in an aqueous medium, in solid form or by high energy milling. The pharmaceutical compositions according to the invention bear an outstanding importance in treatment of cancer.</p>		

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**Inclusion complexes of Taxol or Taxotere or Taxus extract
formed with Cyclodextrins, its preparation and use**

The invention relates to the inclusion complexes of Taxol [2aR-[2a α , 4 β ; 4a β , 6 β , 9 α (α R*, β S*), 11 α -12 α , 12a α , 12b α]]- β -(Benzoylamino)- α -hydroxybenzene-propanoic acid 6,12-b-bis (acetyloxy)-12-(benzoyloxy)-2a, 3, 4, 4a, 5, 6, 9, 10, 11, 12, 12a, 12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca [3,4] -benz-[1,2-b]oxet-9-yl ester or Taxotere (butoxycarbonyl-10-deacetyl-N-debenzoyl taxol) and Taxus extracts (comprising besides taxol other diterpene taxan-derivatives such as cephalomannine, 10-deacetyl-taxol, deacetyl baccatine-III, baccatine-III, cinnamoyl-taxicines, taxusine) formed with a cyclodextrin derivative or cyclodextrin-derivative-mixture.

Even though taxol shows a rather promising biological effectivity and significant antitumor activity, its therapeutical application is associated with a lot of difficulties:

- taxans are very slightly soluble in water, for example the water solubility of taxol is between 0,55-0,59 μ g/ml at 25 °C (determined at Cyclolab)
- taxol is very sensitive to light and the pH, during its decomposition biologically inactive products are forming.
- results given on taxol in pharmacology are challenged of validity because of the cytotoxic solvents used (Cremophor EL) /Denis, J.N: J.Am. Chem. Soc. 110. 5917. 1988 and Fjaellskog M.L. et al.: Lancet, 342-873. 1993 and Webster, L. et al.: J. Natl. Cancer Inst. 85. 1685. 1993./

Numerous processes are known to improve the disadvantageous features mentioned above:

- Using solubilizing agents (mixture of Cremophor EL - anhydrous ethanol in the rate of 1:1, Natl. Cancer Institute, PACLITAXEL Documentation);
- Forming chemically modified micromicelles using phosphatidyl-ethanolamines (Patent of Lipid Specialities, Inc. EP 118 316)
- Using mixtures of ethanol-polysorbates as solubility increasing agents (Patent of Rhone-Poulenc Rorer EP 522 936, and Rhone Poulenc Rorer EP 522 937)
- Using Liposomal taxol formulations (e.g. Aquilar, R. and Raffaelloff, R. WO 93/18751 and Alkan, M.H. et al.: J. Liposome Research 3. 42. 1993.)

There were some trials to increase the water solubility of taxol by forming synthetic derivatives as well.(e.g. written by Zhao, H. et. al. J.Nat. Prod. 54.6. 1607. 1991., Kingston, D.I. Xang, Y.Y. EP Pat. Appl. EP 537905 and Deutsch, H.M. et al. US. pat. 5.157.049)

The biological effectivity of the chemically modified, increased soluble taxol derivatives changes for the worse, mostly the multidrug-resistance shows an upward tendency and the cytotoxicity - just the biological effect - is diminished.

- 5 To solve difficulties during the parenteral application of taxol, Taxol-prodrugs with increased water solubility have also been synthesized. (Matthew A. et. al.: J.Med.Chem. 35. 1. 145 1992.).

- 10 By microencapsulating of taxol Bartoli et. al. wanted to improve the generally poor stability of it (Bartoli H; et. al.: J.Microencapsulation 7.2. 191. 1990).

- 15 There are a lot of difficulties in preparing especially the parenteral pharmaceutical products containing taxol, because the diterpenoid-type, rather lipophilic taxan-derivatives can not be formulated as suitable stable and concentrated solutions even in the presence of large amount of detergents and mixtures of water and organic solvents. /Tarr, B. Pharm. Res. 4.2. 162. 1987./

- 20 Nowadays the officially registered (for example at the National Institutes of Health and the National Cancer Institute) parenteral taxol-forms are formulated as 6 mg/ml concentrated emulsions in polyoxyethylated castor oil (Cremphor EL) and ethanol at the ratio of 1:1, and on application these emulsions have to be diluted to tenfolds. Application of these parenteral products is associated with numerous unpleasant side-effects among others the most important is the serious allergic by-effect caused in consequence of the parenterally hardly tolerable Cremophor EL.
- 25 Moreover the taxol-formulations produced in Cremophor EL - ethanol solvent are not clear solutions but slightly opaline (Trissel, L.A.: Am.J. Hosp. Pharm. 50.300.1993) and at diluting or applying them together with some other pharmaceuticals there is a possibility of the formation of precipitation.

- 30 In a conference in Japan it was reported that glycosyl- and maltosyl- β -cyclodextrins used together with ethanol and ethylacetate increased the solubility of taxol up to 20-110 $\mu\text{g/ml}$ (Mikuni, K. et. al.: 1993.)

- 35 According to our present invention, improved aqueous solubility of Taxol and taxan-derivatives can be reached by using suitable cyclodextrins and/or cyclodextrin derivatives and/or mixtures thereof without forming any chemical bonds between taxol and cyclodextrins.

The inclusion complexes of the present invention can be prepared by

- 5 a.) reacting Taxol or Taxotere or a Taxus extract in an aqueous medium
 with a cyclodextrin derivative and isolating the complex from the mixture
 by means known per se.
 b.) reacting Taxol or Taxotere or a Taxus extract with a cyclodextrin
 derivative in a solid form
 c.) high energy milling of Taxol or Taxotere or a Taxus extract with a
10 cyclodextrin derivative.

The complex can be isolated from the mixture by filtration, centrifugation,
lyophilization, spray-drying, vacuum drying.

- 15 The high energy milling of Taxol or Taxotere or Taxus extract with a cyclodextrin
 derivative can be performed as described or referred to in the published Hungarian
 Patent Application No. T/52366.

- 20 As cyclodextrin derivatives preferably
 - heptakis-2,6-O-dimethyl- β -cyclodextrin
 - randomly methylated- β -cyclodextrin
 - succinyl-methyl- β -cyclodextrin
 - 2-hydroxy propyl- β -cyclodextrin
25 - soluble anionic- β -cyclodextrin (CDPSI)
 - β -cyclodextrin
 - γ -cyclodextrin
 can be used.

- 30 Some of the inclusion complexes of the present invention have improved aqueous
 solubility and stability such as the inclusion complex of Taxol or Taxotere or a
 Taxus extract formed with
 - heptakis-2,6-O-dimethyl- β -cyclodextrin
35 - randomly methylated- β -cyclodextrin
 - succinyl-methyl- β -cyclodextrin
 so they can be used as active ingredients in pharmaceutical compositions.

The pharmaceutical compositions of the invention containing as active ingredient an effective amount of the inclusion complex of Taxol or Taxotere or a Taxus extract formed with a cyclodextrin derivative, preferably heptakis-2,6-O-dimethyl- β -cyclodextrin, randomly methylated- β -cyclodextrin, succinyl-methyl- β -cyclodextrin and customary pharmaceutical filling, diluting and further auxiliary materials can be prepared in a manner known per se.

Other inclusion complexes of the present invention do not or do not significantly improve the aqueous solubility, such as the inclusion complex of Taxol or Taxotere or a Taxus extract formed with

- 2-hydroxy propyl- β -cyclodextrin
- soluble anionic- β -cyclodextrin polymer (CDPSI)
- β -cyclodextrin
- γ -cyclodextrin

but they can be used e.g. to extract taxol from the ferment of taxol producing cells.

The invention is illustrated by the following examples without restricting the invention to them.

Example 1.

11,6 mg of Taxol (Sigma Chemicals Co. USA) is treated in 10 ml of 40% aqueous heptakis-2,6-di-O-methylated β -cyclodextrin at room temperature for 30 minutes, until a solution of slight haze is obtained. This solution is then filtered on sterile 0,22 μ m cellulose acetate membrane filter, resulting in clear aqueous taxol solution in which the dissolved taxol concentration is 992-1000 μ g/ml. (the aqueous solubility of the taxol at 25°C is otherwise 0,55-0,59 μ g/ml)

The clear, sterile filtered aqueous taxol solutions can be stored under normal conditions without deterioration for eight weeks.

The above aqueous taxol solution can be freeze dried resulting in 3,94 g white, slight nearly amorphous solid product, that can be re-dissolved upon contacting with water. The reconstituted solution contains 1000 μ g/ml dissolved taxol, and the pH of this solution is between 5,7-6,2. The existence of inclusion complex in

solid state was proved by X-ray powder diffractometry and by Differential Scanning Calorimetry.

Example 2.

5

Randomly methylated β -cyclodextrin (average degree of substitution=1,8) was dissolved in physiological buffered saline (pH 7,6) at different concentrations and these solutions were incubated with the taxol substrate for 12 hours at room temperature. Each sample contained taxol in 5 mg/ml initial concentration.

10

The suspensions after equilibration were membrane filtered and assayed for dissolved taxol by HPLC. The solubility data obtained are listed in Table 1.

15

Table 1. Aqueous solubility of taxol in randomly methylated β CD solutions of different concentrations.

20

RAMEB (%)	dissolved taxol in μ g/ml
none	0.6
1	4.4
5	42.5
10	231.7
40	859.9

25

This solubility enhancement refers to the complex formation in solution between taxol and methyl- β CD, since glucose did not cause any solubility increase.

Example 3.

30

Taxol was solubilized in the presence of sulfopropoxy- β -cyclodextrin in the same way as described in example 2. The sulfopropoxy- β -cyclodextrin was not found suitable for the solubilization of taxol under investigation conditions (25°C, in water, at neutral pH), in contrast, this derivative was found to interact with taxol in solution unfavorably, and due to this interaction taxol was found to decompose to unknown products.

35

Example 4.

Water soluble anionic- β -cyclodextrin polymer (epichlorohydrin-cross linked carboxymethylated- β -cyclodextrin, abbreviated as CDPSI) was found to be a less potent solubilizing agent than the methylated β -cyclodextrins. The solubility enhancements are listed in Table 2.

Table 2. Aqueous solubility's of taxol in presence of ionic water soluble β -cyclodextrin polymer

	CDPSI (%)	dissolved taxol in $\mu\text{g/ml}$
	0	0.6
	1	1.8
15	5	3.5
	10	10.6
	40	56.8

20

Example 5.

Taxol was solubilized and formulated with 2-hydroxypropylated β -cyclodextrin (HPBCD). The solubility enhancements achieved by HPBCD solutions are given in Table 3.

25

Table 3. Solubilizing of taxol with HPBCD

	HPBCD (%)	dissolved taxol $\mu\text{g/ml}$
30	none	0.6
	0.5	1.0
	1	1.7
	5	6.8
	10	34.9
35	40	100.4

Example 6.

5 Mono-succinyl-methyl- β -cyclodextrin, an acidic function bearing methylated β -cyclodextrin was found to be a potent solubilizing agent for the improvement of aqueous solubility of taxol. In 1 ml of 10 % aqueous solution of succinyl-methyl- β -Cyclodextrin taxol was stirred for 12 hour at room temperature. The suspension was filtered and the dissolved taxol determined by HPLC. The dissolved taxol concentration in 10% aqueous solution of succinyl-methyl- β CD was 244 μ g/ml, while the 40% succinyl methyl- β CD solution enabled a dissolved taxol
10 concentration of 993 μ g/ml. Thus the solubilizing power of monosuccinyl-methyl- β -cyclodextrin was almost as high as that of the heptakis 2,6-di-O-methylated- β -cyclodextrin.

15

Example 7.

8,5 mg of taxol and 26,6 mg (about a 1:2 molar ratio) heptakis-2,6-di-O-methylated- β CD were intensively co-ground with 0,25 ml of ethanol:water 1:2
20 mixture until a homogeneous cream is obtained. The wet cream is dried on air to constant weight, and powdered. The resulting white solid contained 21,8 % taxol.

The in vitro dissolution properties of the entrapped taxol from product according to Example 7 was found to surpass significantly that of the non-complexed taxol, by 120-124 fold. Furthermore the chemical and heat stability of the taxol in this
25 formulation was also improved.

Example 8.

30

8,5 mg of taxol and 52,9 mg of γ -cyclodextrin were stirred intensively in 2,5 ml of 33 % (v/v) aqueous ethanol for 6 hours. The solvent is removed by freeze-drying that results in a white microcrystalline product. In the taxol/ γ -cyclodextrin formulation the taxol had an improved stability against heat as proved by thermal
35 analyses. On the DSC pattern of complex according to Example 8. no sign of the endothermic heat flow is detected in the melting range of taxol, which points to the complexed state of the drug. The crystalline taxol γ CD formulation was found to be suitable for direct tableting. The fact of the formation of novel crystalline lattice was proven by X-ray diffractometry, as well.

The interaction of taxol and γ CD did not result in any solubility enhancement, in contrast the effect of γ CD was just opposite, thus the aqueous γ CD solutions are able to remove taxol from multicomponent mixture (e.g. from *Taxus brevifolia* ground stem bark) by formation of stable crystalline complex, from which the entrapped taxol can be re-extracted.

Example 9.

50 mg of β -cyclodextrin and 8,5 mg of taxol were reacted in 2,5 ml of water-ethanol 1:2 mixture at room temperature for 12 hours. The solvent was removed by spray-drying or freeze-drying yielding a white microcrystalline solid, that revealed to novel crystalline state thus an inclusion complex by X-ray powder diffraction. The solid taxol/ β -cyclodextrin formulation was found to be suitable for direct tableting. The in vitro dissolution rate of taxol from β CD formulation was found to be better, than that of the free taxol both in water and in pH 7,6 buffer.

Example 10.

The solubilization of a synthetic taxol analog, Taxotere (butoxycarbonyl-10-deacetyl-N-debenzoyl taxol) was carried out by stirring intensively the 2,5 mg of Taxotere in 1 ml of 40 % aqueous randomly methylated- β -cyclodextrin (DS=1,8) at 25° C for 12 hours. The solubility enhancement achieved by this way was 850 times that of the free taxol derivative in water. The freeze dried product according to Example 10 is a white amorphous powder, that showed a good wettability and improved aqueous solubility under normal conditions. The solubility enhancement achieved by methylated β -cyclodextrin proved the existence of inclusion complex in solution. (The same concentration of glucose did not improve the solubility of Taxotere.)

Example 11.

A dilutable concentrated solution containing taxol and solubilizer according to the present invention:

- 5 10 mg taxol (Sigma Chemicals No. T-7402, Lot. No.23H0464)
 10 ml 40 % aqueous solution of crystalline heptakis 2,6-di-O-methyl/ β -cyclodextrin

- are stirred for 12 hours under nitrogen, protected from light. The resulting clear solution is then sterile filtered across a 0,22 μ m membrane into a sterile injection
10 ampoule and sealed. The sterile solution is useful for further dilution with physiologically acceptable diluents to desired concentration and the solution is stable for two months. (the loss of active ingredient in solution after a 60-day storage at 25° C was found to be less, than 3%)

15

Example 12.

- Taxol containing hydrogel is prepared by dissolving 1 mg of taxol (Sigma Chemicals No. T-7402, Lot.No. 23H0464) in 1 ml of 40 % randomly methylated- β
20 -cyclodextrin and this solution is mixed with 25 mg of methyl cellulose exhaustively for 30 minutes to obtain a transparent colorless topical useful gel which has no irritation to human skin and preserves well the dissolved taxol.
-

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What we claim is:

1. Inclusion complex of Taxol [2aR-[2a α , 4 β ; 4a β , 6 β , 9 α (α R*, β S*), 11 α -12 α , 12a α , 12b α]]- β -(Benzoylamino)- α -hydroxybenzene-propanoic acid 6,12-b-bis
5 (acetyloxy)-12-(benzoyloxy)-2a, 3, 4, 4a, 5, 6, 9, 10, 11, 12, 12a, 12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca [3,4]-benz-[1,2-b]oxet-9-yl ester or Taxotere (butoxycarbonyl-10-deacetyl-N-debenzoyl taxol) or Taxus extracts formed with a cyclodextrin derivative.
10
2. Inclusion complex of Taxol with a cyclodextrin derivative.
3. Inclusion complex of a Taxus brevifolia solvent free extract comprising besides Taxol other diterpene taxan-derivatives such as cephalomannine, 10-deacetyl-
15 taxol; deacetyl baccatine-III; baccatine-III, cinnamoyl-taxicines; taxusine etc. with a cyclodextrin derivative.
4. Inclusion complex of Taxol or Taxotere or a Taxus brevifolia extract formed with heptakis-2,6-O-dimethyl- β -cyclodextrin having improved aqueous solubility
20 and stability.
5. Inclusion complex of Taxol or Taxotere or a Taxus brevifolia extract formed with randomly methylated- β -cyclodextrin having improved aqueous solubility and
25 stability.
6. Inclusion complex of Taxol or Taxotere or a Taxus brevifolia extract formed with succinyl-methyl- β -cyclodextrin having improved aqueous solubility and
stability.
- 30 7. Inclusion complex of Taxol or Taxotere or a Taxus brevifolia extract formed with 2-hydroxy propyl- β -cyclodextrin.
8. Inclusion complex of Taxol or Taxotere or a Taxus brevifolia extract formed with soluble anionic- β -cyclodextrin-polymer (CDPSI) /average molecular weight
35 36-8000./
9. Inclusion complex of Taxol or Taxotere or a Taxus brevifolia extract formed with β -cyclodextrin.

10. Inclusion complex of Taxol or Taxotere or a *Taxus brevifolia* extract formed with γ -cyclodextrin.

5 11. Process for the preparation of the inclusion complex of Taxol or Taxotere or a *Taxus brevifolia* extract formed with a cyclodextrin-derivative which comprises

a.) reacting Taxol or Taxotere or a *Taxus brevifolia* extract in an aqueous medium with a cyclodextrin derivative and isolating the complex from the mixture by means known per se.

10 b.) reacting Taxol or Taxotere or a *Taxus brevifolia* extract with a cyclodextrin derivative in a solid form

c.) high energy milling of Taxol or Taxotere or a *Taxus brevifolia* extract with a cyclodextrin derivative.

15 12. Process according to claim 11, characterized by, that the complex is isolated from the mixture by filtration, centrifugation, lyophilization, spray-drying, vacuum drying.

20 13. Pharmaceutical composition comprising as active ingredient an effective amount of the inclusion complex of Taxol or Taxotere or a *Taxus* extract formed with a cyclodextrin derivative, preferably heptakis-2,6-O-dimethyl- β -cyclodextrin, randomly methylated- β -cyclodextrin, succinyl-methyl- β -cyclodextrin and conventional pharmaceutical filling, diluting and further auxiliary materials.

25 14. Method of treatment of cancer in humans orally, parenterally which comprises administering to the human an effective amount of an inclusion complex of Taxol or Taxotere or *Taxus* extract formed with a cyclodextrin derivative preferably heptakis-2,6-O-dimethyl- β -cyclodextrin, randomly methylated- β -cyclodextrin, succinyl-methyl- β -cyclodextrin.

30 15. Use of inclusion complexes of Taxol or Taxotere or *Taxus* extracts formed with cyclodextrin derivatives, preferably 2-hydroxy-propyl- β -cyclodextrin, soluble anionic- β -cyclodextrin-polymer, β -cyclodextrin, γ -cyclodextrin, most preferably γ -cyclodextrin to extract taxol from the fermentation broth of taxol producing cell cultures.

35

INTERNATIONAL SEARCH REPORT

International application No.

PCT/HU 94/00012

A. CLASSIFICATION OF SUBJECT MATTER

IPC⁵: C 07 D 305/14; A 61 K 31/335

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁵: C 07 D 305/14; A 61 K 31/335

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS WPIL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 5 059 699 (KINGSTON et al.) 22 October 1991 (22.10.91), claims 1,3,5.	1-15
P,A	AU, B, 645 927 (ENSUIKO SUGAR REFINING COMPANY) 27 January 1994 (27.01.94), claims 1-5, table 1. -----	1-15

☐ Further documents are listed in the continuation of Box C.
 ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search

13 Sept mber 1994 (13.09.94)

Date of mailing of the international search report

21 September 1994 (21.09.94)

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/HU 94/00012

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 14 (Rule 39.1 (iv) PCT)
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 14 is considered to be a method for the treatment of the human or animal body by therapy, all claims have been searched completely. Relevant documents are cited within the search report.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ N protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/HU 94/00012

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
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